Although hypertension is a common trait, its etiology and pathogenesis are not well understood. Despite the increasing understanding of rare Mendelian forms of hypertension, the common variety of hypertension is likely to be a complex trait, with both hereditary and environmental determination.

In the face of significant heritability yet uncertain mode of inheritance, a useful strategy may be to establish so-called “intermediate phenotypes” (Figure): ideally, simple Mendelian or monogenic traits that are associated with hypertension. The disorder may result from alterations in more than one gene, as well as different genes in subgroups of hypertensive subjects; hence, a particular intermediate phenotype may be present in all or only in a subgroup of essential hypertensives. Such a monogenic trait might be more directly determined by the action of a particular gene and, hence, subject to less environmental influence than a complex phenotype such as blood pressure. Thus, an intermediate phenotype might be helpful in identifying those offspring of essential hypertensives who have inherited susceptibility alleles predisposing them to later development of hypertension.

Evidence is accumulating for alteration of autonomic function in essential hypertension, especially activation of the sympathetic nervous system, which may be involved in not only the genesis of blood pressure elevation but also the progression of target-organ damage. Adrenergic regulation of blood pressure may be altered not only in hypertensives themselves, but also in their (normotensive) first-degree relatives (siblings and offspring): reported adrenergic disturbances in family members include diminished secretion of the catecholamine release-inhibitory peptide catestatin, exaggerated cardiovascular response to catecholamines, and mental stress, and alterations in catecholamine release into the bloodstream. Understanding the genes that influence variation in autonomic function, therefore, will contribute to untangling the multigenic disorders of hypertension. Indeed, multiple genetic loci are likely to contribute to common variations in autonomic function and, hence, to human blood pressure.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Family History of Hypertension and Intermediate Phenotypes

Family history of hypertension is a powerful risk factor for future development of the disease, with progressive increments in risk as a function of number of parents positive and younger parental age of onset. Family history stratification of younger (age 20 to 40 years) individuals, even with normal blood pressure, also yields significant differences in pathogenic phenotypes in a number of important physiological domains impinging on blood pressure (Table): adrenergic, renal, oxidative, metabolic, and vascular.

Such early derangement of multiple physiological systems in human hypertension is paralleled by similarly global changes in patterns of gene expression in rodent genetic models of hereditary hypertension after systems biology analyses of the adrenal transcriptome in such models of the human disease.

The Current Report: Autonomic Function in BP Tertiles of a Young, Normotensive Population

In this issue of Hypertension, Flaa et al studied biochemical and physiological measures of sympathetic activity in a group of healthy, 19-year-old males drawn from >4000 military recruits in Norway. From this population-based sample, they selected 130 men from 3 subsets of phenotypic extremes for more intensive study, based on tertiles of mean arterial BP: 1st percentile, 50th percentile, and 98th to 99th percentile. The objective of the study was to compare blood pressure and catecholamines at rest and in response to stressors (cold pressor test, mental stress test, and orthostatic stress test) across the 3 groups. Flaa et al found that basal catecholamines directly paralleled blood pressure group and that the effects of mental stress differed across the groups, with the highest BP stratum exhibiting increased hemodynamic and catecholamine responses to stress.

This study can be viewed as a successful attempt to understand how precursor traits to hypertension cluster within the normotensive population. As in any complex trait with multiple phenotypic manifestations, it may be difficult to impute cause and effect relationships among multiple correlated traits. Flaa et al identify a group of individuals who have not only relatively high (though not “hypertensive”) baseline blood pressure, but also greater basal catecholamines and mental stress-induced increments in blood pressure and catecholamines; but which of these traits is primary in the pathway to disease? Is the response to mental stress a result of having higher baseline blood pressure? Or, do recurrent exaggerated adrenergic responses to mental stress, in genetically susceptible individuals, ultimately eventuate in sustained hypertension, as suggested by the Folkow hypothesis? One advantage of the approach of Flaa et al is the
study of subjects with still-normal blood pressure; in such individuals, phenotypic clusters cannot readily be ascribed to the late consequences of prolonged hypertension.

Studies of trait heritability and, ultimately, associated genetic variants, may be required to unravel the “Gordian knot” posed by such phenotypic clusters. Family history or twin studies may be especially useful in such a complex setting. Family history approaches have provided evidence for the role of heredity in augmented stress responses of subjects at genetic risk of hypertension. The “intermediate phenotypes” that are putative precursors to hypertension may share genetic determination, and thus be amenable to analysis of genetic covariance (ie, the cross product of the heritability of 2 traits, a measure of genetic pleiotropy).

In research on twin pairs, one can probe the shared genetic determination (pleiotropy) between pairs of precursor traits for hypertension, either by computing the genetic covariance or by using bivariate/MANOVA approaches, testing whether a particular genotype coordinately determines 2 traits.

**Early Phenotypic Alterations in Hypertension: Changes in Individuals at Genetic Risk of Hypertension**

<table>
<thead>
<tr>
<th>System</th>
<th>Example</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenergic</td>
<td>Exaggerated pressor response to adrenergic compounds</td>
<td>5, 6, 9</td>
</tr>
<tr>
<td></td>
<td>Increased frequency of tyrosine hydroxylase activating genotype</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Exaggerated pressor response to mental stress</td>
<td>7, 8</td>
</tr>
<tr>
<td>Nicotinic</td>
<td>Diminished catestatin (endogenous antagonist of catecholamine release)</td>
<td>4</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>Increased amylin (insulin antagonist)</td>
<td>17</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Diminished large arterial compliance</td>
<td>18</td>
</tr>
<tr>
<td>Vascular</td>
<td>Increased H2O2</td>
<td>16</td>
</tr>
<tr>
<td>Oxidative</td>
<td>Diminished glomerular reserve with hyperfiltration; increased microalbumin excretion; decreased kallikrein (KLK1) excretion</td>
<td>14, 15</td>
</tr>
</tbody>
</table>

Interpretation: Implications for the Pathogenesis of Hypertension

The study by Flaa and colleagues concerned largely healthy, younger (age 19 years) individuals, with group basal blood pressures ranging from 116/62 to 137/74 mm Hg. Therefore, this population does not allow a direct test whether their autonomic traits predispose to later development of hypertension. However, longitudinal studies in human populations now clearly document that normotensive individuals in the higher blood pressure strata are at increased risk to progress to hypertension. Indeed even “pre-hypertension” (in the BP stratum 120 to 139/80 to 89 mm Hg) in a population-based cohort is a predictor of elevated cardiovascular morbidity.

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**References**

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